

Attachment 20



October 15, 2019

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Tobacco Products; Required Warnings for Cigarette Packages and
Advertisements (Docket No. FDA-2019-N-3065)

Dear Sir or Madam:

ITG Brands, LLC (“ITGB”), a leading manufacturer and distributor of tobacco products, including cigarettes, and a Subsequent Participating Manufacturer to the multi-state Master Settlement Agreement (“MSA”), submits the following comments to the above-referenced docket in response to the U.S. Food and Drug Administration’s (“FDA’s” or the “Agency’s”) proposed rule, Tobacco Products; Required Warnings for Cigarette Packages and Advertisements (the “Graphic Warnings Proposed Rule”). ITGB has long been deeply engaged on regulatory and scientific issues before FDA, including with respect to the design of consumer perception studies to evaluate cigarette graphic health warnings.¹ We have consistently encouraged the Agency to exercise the same rigor in the design, conduct, and analysis of its consumer perception and behavioral studies respecting the potential mandatory disclosures and warnings as the Agency expects industry to exercise in the context of Premarket Tobacco Product Applications (“PMTAs”) or Modified Risk Tobacco Product Applications (“MRTPAs”).² In both contexts, ITGB is committed to promoting public awareness of truthful and not misleading information about the harms associated with smoking cigarettes, including through appropriate warnings. However, ITGB does not believe that the Agency has exercised the expected rigor with respect to the Graphic Warnings Proposed Rule, and as a consequence the warnings it has proposed would be misleading and run afoul of the First Amendment.

¹ See, e.g., SMARTT Coalition, Comment Letter on Agency Information Collection Activities, Proposed Collection, Comment Request (May 30, 2017), <https://www.regulations.gov/document?D=FDA-2017-N-0932-0014>; SMARTT Coalition, Comment Letter on Request for Comments on Experimental Study of Graphic Cigarette Warning Labels (Apr. 22, 2010), <https://www.regulations.gov/document?D=FDA-2010-N-0079-0003>.

² See SMARTT Coalition, Comment Letter on Agency Information Collection Activities, Proposed Collection, Comment Request at 2 (May 30, 2017), <https://www.regulations.gov/document?D=FDA-2017-N-0932-0014> (“SMARTT urges FDA to take into account the design characteristics and methodological issues identified in the Agency’s evaluation of [Swedish Match North America’s] consumer perception study which, if left unaddressed, could dramatically limit the ability of the study to evaluate consumer understanding, including the primary study outcomes of beliefs and knowledge of the negative health consequences of smoking.” (emphasis omitted)).

cancer attributable to smoking. The National Cancer Institute estimates that the number of “new cases of bladder cancer [per year is] 20.1 per 100,000 men and women . . .”⁵⁷ Even if FDA’s estimate that approximately 40 percent of bladder cancer is attributable to smoking is correct,⁵⁸ this suggests the annual risk of developing bladder cancer attributable to smoking is approximately 8.04 per 100,000, or 0.00804 percent.

The administrative record also demonstrates that FDA did not consider perceptions of the relative risk of bladder cancer caused by smoking (i.e., as compared to the background risk from other causal factors) in developing the proposed warning. Likewise, the administrative record shows no indication that FDA considered, or tested consumer understanding of, the nature of the relationship of smoking on bladder cancer risk. For instance, the proposed warning fails to convey, and the administrative record does not indicate that the Agency tested consumers’ understanding that, the relationship between number of cigarettes smoked daily and bladder cancer incidence is not purely linear. Specifically, a “risk plateau” has been observed in which “very heavy smokers . . . do not experience a markedly increased risk [of bladder cancer] compared with less heavy smokers.”⁵⁹ Further, in support of its proposed warning, FDA also cites literature in which the association between bladder cancer and consistent smoking of up to ten cigarettes per day was not statistically significant.⁶⁰

- ***Newborn infant weighing four pounds.*** The Agency proposes to pair the text “WARNING: Smoking during pregnancy stunts fetal growth” with a photorealistic image of a “newborn infant on a medical scale, and the digital display on the scale reads four pounds.”⁶¹ First, as identified in the 2010 Surgeon General’s report, “[f]etal growth cannot be directly assessed,” and while birth weight has been used as a surrogate endpoint for fetal growth, birth weight “reflects not only growth but

⁵⁷ Nat’l Cancer Inst., Cancer State Facts: Bladder Cancer, <https://seer.cancer.gov/statfacts/html/urinb.html> (last visited Oct. 15, 2019).

⁵⁸ FDA states that 40 percent of bladder cancer deaths in 2000 through 2004 were attributable to smoking, and puts forward no data or rationale to indicate whether the mortality rate of bladder cancers attributable to smoking differ from bladder cancer attributable to other causes. See 84 Fed. Reg. at 42,774. We therefore use FDA’s 40 percent figure, *ad arguendo*, to estimate the proportion of new bladder cancers attributable to smoking.

⁵⁹ Frits van Osch, *et al.*, *Modeling the Complex Exposure History of Smoking in Predicting Bladder Cancer: A Pooled Analysis of 15 Case-Control Studies*, 30 EPIDEMIOLOGY 458, 458-465 (2019), <https://onlinelibrary.wiley.com/doi/epdf/10.1002/ijc.31059>.

⁶⁰ See 84 Fed. Reg. at 42,774 (citing Maki Inoue-Choi, *et al.*, *Association Between Long-Term Low-Intensity Cigarette Smoking and Incidence of Smoking-Related Cancer in the National Institutes of Health-AARP Cohort.*, 142 INT’L J. OF CANCER, 271-280 (2018), and Frits van Osch, *supra* note 59, at 458-465).

⁶¹ 84 Fed. Reg. at 42,774.

also gestational age, as well as genetic potential, which is not commonly assessed.”⁶²

Further, with respect to birth weight, while the 2010 Surgeon General’s Report indicates that infants of smokers are roughly twice as likely as those of nonsmokers to be low birth weight,⁶³ this proposed warning does not convey, and the administrative record indicates that FDA did not evaluate consumer perception of, the estimated 8.17 percent baseline risk of low birthrate across all pregnancies.⁶⁴ Nor does the proposed warning accurately depict a typical low birth weight attributable to smoking. The 2010 Surgeon General’s Report defines low birth weight as any birth weight of less than 2,500 grams (approximately 5.51 pounds),⁶⁵ and states that the “[i]nfants of smokers typically weigh 150 to 200 g[rams] less than infants of nonsmokers.”⁶⁶ The proposed warning instead depicts an infant that weighs four pounds, or approximately 686 grams less than the low end of normal birth weight.

- **Chest incision.** The Agency proposes to pair the text “WARNING: Smoking can cause heart disease and strokes by clogging arteries” with a photorealistic image of “the chest of a man . . . wearing a large open hospital gown . . . [who has] a large, recently sutured incision running down the middle of his chest and is undergoing post-operative monitoring.”⁶⁷ The proposed warning does not reflect, and the administrative record does not indicate that FDA assessed consumer understanding of, the baseline risk for stroke, heart disease, or the need for coronary bypass or open heart surgery. Indeed, FDA acknowledges in the Graphic Warnings Proposed Rule that 75.9 percent of heart disease deaths and 88.7 percent of stroke deaths are not attributable to smoking.⁶⁸ Cardiovascular disease risk factors include obesity, hypertension, diabetes mellitus, chronic kidney disease, and high low-density lipoprotein (“LDL”) cholesterol.⁶⁹

The proposed warning appears to depict coronary bypass or open heart surgery which is a worst case, rather than representative, scenario. In general, inpatient discharges for coronary bypass after grafting decreased from 683,000 in 1997 to

⁶² CTR. FOR DISEASE CONTROL & PREVENTION, HOW TOBACCO SMOKE CAUSES DISEASE, THE BIOLOGY AND BEHAVIORAL BASIS FOR SMOKING-ATTRIBUTABLE DISEASE: A REPORT OF THE SURGEON GENERAL, ch. 8, at 538 (2010).

⁶³ *Id.*

⁶⁴ Joyce A. Martin, *et al.*, *Births: Final Data for 2016*, NAT’L VITAL STATISTICS REP., at 1-55 (2018), https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_01.pdf.

⁶⁵ CTR. FOR DISEASE CONTROL & PREVENTION, *supra* note 62, ch. 8, at 538.

⁶⁶ *Id.*

⁶⁷ 84 Fed. Reg. at 42,774.

⁶⁸ *Id.* at 42,775.

⁶⁹ See Donna K. Arnett, *et al.*, 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, 74 AM. C. OF CARDIOLOGY E177, E177-E232 (Sept. 10, 2019), <http://www.onlinejacc.org/content/accj/74/10/e177.full.pdf>.

371,000 in 2014.⁷⁰ Notably, the Graphic Warnings Proposed Rule does not address or provide any data regarding the incidence of coronary bypass among smokers.

- ***Diseased, darkened lungs.*** The Agency proposed to pair the text “WARNING: Smoking causes COPD, a lung disease that can be fatal” with a photorealistic image of “gloved hands holding . . . diseased, darkened lungs.”⁷¹ The Graphic Warnings Proposed Rule contains no discussion regarding the relationship between smoking and the image in the proposed rule. Moreover, the proposed warning fails to convey the relationship between cigarette use topography and the depicted image.⁷² The proposed warning fails to convey that such lung pigmentation is unlikely to occur except after “many years” of “heavy” smoking.⁷³
- ***Nasal canula and oxygen tank.*** The Agency proposes to pair the text “WARNING: Smoking causes COPD, a lung disease that can be fatal” with a photorealistic image of “the head and neck of a man . . . who has a nasal canula under his nose supplying oxygen; the oxygen tank can be seen behind his left shoulder.”⁷⁴ FDA estimates that, among the 189.776 million “ever smokers”, approximately 7.5 million people, or 3.9 percent, currently have (diagnosed or undiagnosed) COPD attributable to smoking.⁷⁵

Long term-oxygen therapy, delivered through a nasal canula, as depicted in the proposed warning, is one of several treatments for COPD.⁷⁶ For example, the Mayo Clinic’s practice guidelines recommend long-term oxygen therapy only for a subset of patients with a resting oxygen saturation of 88 percent or less.⁷⁷ **Again, the proposed warning depicts a ‘worst case scenario,’ without any discussion in the administrative record of the proportion of smokers developing COPD who will require long-term oxygen therapy (or home oxygen), much less the proportion of all smokers who will require home oxygen.**

- ***Erectile dysfunction.*** The Agency proposes to pair the text “WARNING: Smoking reduces blood flow, which can cause erectile dysfunction” with a “photorealistic image depicting a man who is experiencing erectile dysfunction . . . sitting on the edge of a bed and leaning forward, with one elbow resting on each knee. The man’s

⁷⁰ Emelia J. Benjamin, *et al.*, *Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association*, CIRCULATION, Mar. 5, 2019, at e511, <https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000659>.

⁷¹ 84 Fed. Reg. at 42,775.

⁷² *See, e.g.*, Farber Decl. ¶ 5 (“The amount of black pigmentation in the [similar secondhand smoke] graphic image would likely result from *many years* of *heavy* direct smoking.” (emphasis added)).

⁷³ *Id.*

⁷⁴ 84 Fed. Reg. at 42,775.

⁷⁵ *Id.* at 42,776.

⁷⁶ *See* Shireen Mirza, *et al.*, *COPD Guidelines: A Review of the 2018 Gold Report*, 93 MAYO CLINIC 1488, 1493-94 (Oct. 2018), [https://www.mayoclinicproceedings.org/article/S0025-6196\(18\)30409-9/pdf](https://www.mayoclinicproceedings.org/article/S0025-6196(18)30409-9/pdf).

⁷⁷ *See id.*

head is tilted down, with his forehead pressed into the knuckles of his right hand. Behind him on the bed, his female partner looks off in another direction.”⁷⁸

The proposed warning does not convey either the absolute or relative risk of erectile dysfunction associated with smoking, and the Agency did not include assessments of consumers’ understanding of absolute and relative risk in the design of its consumer perception studies. The Agency references literature indicating that erectile dysfunction is a common condition in the general population.⁷⁹ In support of the statement that “[s]mokers have been found to have a 40 percent increased risk of erectile dysfunction,”⁸⁰ the Agency cites a study which found that the correlation coefficient between erectile dysfunction and smoking “after adjusting for age . . . was attenuated, -0.09 ($p < 0.02$).”⁸¹

- ***Feet with several amputated toes.*** The Agency proposes to pair the text “WARNING: Smoking reduces blood flow to the limbs, which can require amputation” with a “photorealistic image depicting the feet of a person who had several toes amputated due to tissue damage resulting from peripheral vascular disease . . .” also known as peripheral arterial disease.⁸² This depiction of the risks of peripheral vascular disease is fundamentally misleading; the prevalence of peripheral vascular disease in patients who have *no symptoms at all* is high, ranging from 20 to over 60 percent of patients.⁸³ Indeed, the “natural history of lower extremity outcomes in people with [peripheral arterial disease] has been described as ‘benign.’ This is in part because only a small proportion of patients” require amputation.⁸⁴ Over a five year period, only one or two percent of patients with peripheral vascular disease will *either* develop critical limb ischemia *or* require amputation.⁸⁵

⁷⁸ 84 Fed. Reg. at 42,776.

⁷⁹ See *id.* (“[A]t least 20 percent of all men have some degree of erectile dysfunction. Among men between the ages of 40 and 70 years, approximately 50 percent have some degree of erectile dysfunction.” (citations omitted)).

⁸⁰ *Id.*

⁸¹ Naomi M. Gades, *et al.*, *Association Between Smoking and Erectile Dysfunction: A Population Based Study*, 161 AM. J. OF EPIDEMIOLOGY 346, 348 (Feb. 2005), <https://academic.oup.com/aje/article/161/4/346/92680>. The Agency also cites to a “meta-analysis” of one cohort study and nine-cross sectional studies which found the “summary odds ratio of ED for an increase of 10 cigarettes smoked per day was 1.14 (95% confidence interval 1.09 to 1.18), with moderate heterogeneity ($P = 0.061$, $I^2 = 44.7\%$). For an increment of 10 years of smoking, the combined odds ratios of ED was 1.15 (95% confidence interval 1.10 to 1.19), without substantial heterogeneity ($P = 0.522$, $I^2 = 0.0\%$).” Shiyi Cao, *et al.* *Association of Quantity and Duration of Smoking with Erectile Dysfunction: A Dose-Response Meta-Analysis.* 11 J. OF SEXUAL MED., 2376, 2376-2384 (Oct. 2014), <https://doi.org/10.1111/jsm.12641>.

⁸² 84 Fed. Reg. at 42,776.

⁸³ See Mary McGrae McDermott, *Lower Extremity Manifestations of Peripheral Artery Disease: The Pathophysiologic and Functional Implications of Leg Ischemia*. 116 CIRCULATION RES. 1540, 1540-50 (Apr. 24, 2015), <https://www.ahajournals.org/doi/pdf/10.1161/CIRCRESAHA.114.303517>.

⁸⁴ *Id.* at 1545 (citations omitted).

⁸⁵ See *id.*

The administrative record indicates that the Agency did not assess consumer perception of the absolute or relative risk of peripheral vascular disease among smokers. Similarly, the Graphic Warnings Proposed Rule does not address the likelihood that smokers *will require amputation*, as depicted in the proposed warning. Indeed, this proposed warning is misleading because it depicts a condition—peripheral vascular disease characterized by reduced blood flow to multiple limbs—that is exceedingly rare among smokers, affecting no more than one in 1,000 smokers.⁸⁶

- **High blood sugar.** The Agency proposes to pair the text “WARNING: Smoking causes type 2 diabetes, which raises blood sugar” with a “photorealistic image depicting a personal glucometer device being used to measure the blood glucose level of a person with type 2 diabetes The digital display reading of 175 mg/dL and a notation on the glucometer indicate a high blood sugar level.”⁸⁷ Diabetes is defined as a fasting blood sugar of greater than or equal to 126 mg/dL.⁸⁸ A fasting blood sugar level of 175 mg/dL is well in excess of this threshold. **Further, as with the other warnings, the proposed warning is misleading in that it does not convey either the absolute or relative risk of diabetes as a result of smoking. Indeed, FDA acknowledges that the vast majority—87.3 percent—of diabetes related deaths are not attributable to smoking at all.**⁸⁹
- **Needle in eye.** FDA proposes to pair the text “WARNING: Smoking causes age-related macular degeneration, which can lead to blindness” with a photorealistic image of a “man [] receiving an injection in his right eye to prevent additional vessel growth.”⁹⁰ The Graphic Warnings Proposed Rule acknowledges that the prevalence of any macular degeneration among adults over age 40 years is estimated to be 6.5 percent,⁹¹ but FDA did not assess whether consumers viewing the proposed warning understood the absolute risk of macular degeneration in general, or among smokers. Macular degeneration “is a multifactorial disorder” for which genetics, sunlight, diet, cardiovascular factors, and alcohol are also potential risk factors.⁹² Yet FDA failed to conduct consumer perception research to assess whether consumers understood the multifactorial nature of macular degeneration and, therefore, the relative risk of macular degeneration among smokers.

Nor is the depiction of treatment of macular degeneration accurate; the needle depicted is thicker than one that would actually be used to treat macular

⁸⁶ Comment of RAI, Exhibit K, Decl. of Robert Wagmeister, M.D. ¶¶ 3-4 [hereinafter “Wagmeister Decl.”].

⁸⁷ 84 Fed. Reg. at 42,776.

⁸⁸ See AM. DIABETES ASS’N DIAGNOSIS, <https://www.diabetes.org/a1c/diagnosis> (lasted visited Oct. 15, 2019).

⁸⁹ 84 Fed. Reg. at 42,777.

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² Richard A. Armstrong and Maryam A. Mousavi, *Overview of Risk Factors for Age-Related Macular Degeneration (AMD)*, 10 J. STEM CELLS 171, 171-91 (Jan. 2015).